SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho Biotech Clinical Affairs, L.L.C. NAME OF FINISHED PRODUCT: Epoetin alfa NAME OF ACTIVE INGREDIENT(S): Epoetin alfa	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: PR03-27-064

Title of Study: A Randomized, Open-Label Study of PROCRIT® (Epoetin Alfa) Initiated at 40,000 Units Every Week Versus 80,000 Units Every Two Weeks in Anemic Patients With Cancer Receiving Chemotherapy

Principal Investigator: David H. Henry, M.D., Pennsylvania Oncology Hematology Associates, Philadelphia, PA.

Publication (Reference): Henry, DH, Xie J, Woodman RC. Randomized, open-label study of epoetin alfa 40,000 U once weekly versus 80,000 U every two weeks in anemic patients with cancer receiving chemotherapy. *Blood* 2005; 106(11): 21b; Abstract 3772.

Study Initiation/Completion Dates: 30 June 2004 to 02 August 2005. **Phase of development:** 2b

Objectives: The primary objective of the study was to compare end of study hemoglobin (Hb) level between PROCRIT 40,000 units (U) administered subcutaneously (SC) once every week (QW) and 80,000 U SC every 2 weeks (Q2W) in anemic patients with cancer receiving chemotherapy. Secondary objectives were to assess the Hb response, time to Hb response, transfusion requirements, and safety.

Methodology: This was a prospective, randomized, open-label, multicenter study to compare the efficacy and safety of an 80,000 U Q2W epoetin alfa regimen to the approved dosing regimen of 40,000 U QW when administered for up to 12 weeks to patients with chemotherapy-induced anemia.

Dosing and Dose Adjustments. Patients who provided written informed consent and met study eligibility criteria were randomly assigned in a 1:1 ratio to receive epoetin alfa at a starting dose of 80,000 U SC Q2W or 40,000 U SC QW. Dose adjustment was based on Hb response. Dose escalation to 60,000 U QW was permitted for nonresponders (Hb increase <1 g/dL after 4 weeks) in the 40,000 U QW group. In the 80,000 U Q2W group, a dose modification to 40,000 U SC QW was required if, at any time, Hb decreased by ≥1 g/dL from baseline; if the Hb level had not increased by at least 1 g/dL after 4 weeks of therapy at this weekly dose, the dose was increased to 60,000 U SC QW. In both epoetin alfa groups, the dose of study drug was withheld if Hb was increased to > 13 g/dL, and then re-initiated with a 25% dose reduction when Hb became ≤12 g/dL (i.e., from 80,000 U Q2W to 60,000 U Q2W; 60,000 U QW to 40,000 U QW; 40,000 U QW to 30,000 U QW). A similar dose reduction was required in the event that Hb rose to >12 g/dL or increased too rapidly (>1.0 g/dL in a 2-week period). A confirmatory Hb measurement was obtained within 24 hours prior to withholding or adjusting the epoetin alfa dose. If the Hb level dropped by ≥1 g/dL from the Hb level at the time of dose reduction, the dose could be re-escalated to the previous dose. All patients received oral ferrous sulfate 325 mg once daily or an equivalent formulation as tolerated. Red blood cell (RBC) or packed red blood cell (pRBC) transfusions could be given at the discretion of the investigator.

Study treatment was administered for up to 12 weeks during chemotherapy administration. All patients were followed weekly until 2 weeks after the last dose of epoetin alfa or up to a maximum of 13 weeks on study, whichever came first.

Number of Patients (planned and analyzed): The required sample size was 280 to provide a power of 80% for demonstrating noninferiority of the mean change in Hb from baseline to the end of study (EOS) in Hb for the 80,000 U Q2W regimen relative to the 40,000 U QW regimen. A total of 298 patients were randomized, received study treatment, and analyzed for safety (safety/intent-to-treat [ITT] population). Analysis of the primary efficacy endpoint was performed for both the per protocol population (N=145) and the modified intent-to-treat (mITT) population (N=295).

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Diagnosis and Main Criteria for Inclusion: Patients were to be men or women at least 18 years of age, have a histologically-confirmed non-myeloid malignancy, scheduled to receive cyclic chemotherapy for at least 12 weeks after enrollment, and have an Hb concentration of ≤11 g/dL. Patients who had received any erythropoietic agent within the previous 3 months, for whom non-palliative radiation therapy was planned during the study period, and who had received a transfusion of platelets or pRBC within the 28 days prior to the first dose of epoetin alfa were excluded. Patients were to have an ECOG performance status score of 0 to 2, a life expectancy of at least 6 months, and adequate renal, hepatic, and hematologic function.

Test Product, Dose and Mode of Administration, Batch No.: Epoetin alfa (PROCRIT®) was supplied as a single use, 1-mL vial containing 40,000 units of epoetin alfa and 2.5 mg human albumin. In the QW group, the starting dose was 40,000 U by SC injection, and the dose could not exceed 60,000 U QW. In the Q2W group, the starting dose was 80,000 U by SC injection, and the dose could not exceed 80,000 U Q2W. Lot numbers for epoetin alfa were R12743, R12699, R12915, and R12489 (NDC #59676-340-01).

Duration of Treatment: 12 weeks.

Criteria for Evaluation:

Efficacy: The primary endpoint was the mean change in Hb from baseline to EOS; the EOS value was defined as the final Hb level for a patient, taken within 2 weeks after the last dose of epoetin alfa or at Week 13, whichever came first. Secondary efficacy endpoints were the proportion of patients achieving ≥1 g/dL or ≥2 g/dL increase in Hb not attributable to a pRBC or whole blood transfusion by week for Week 5 to 13 and the time to these Hb responses; the proportion of patients achieving a ≥2 g/dL Hb increase or a Hb of 12 g/dL by week for Week 5 to 13 and the time to this Hb response; the change from baseline in Hb over time; the proportion of patients receiving a pRBC transfusion overall, between Week 5 and 13, and between Week 1 to 4, Week 5 to 8 and Week 9 to 13; the number of units transfused; and the proportion of patients who had a change in dosing regimen from Q2W to QW administration during the study.

Safety: Safety parameters included the incidence of deaths, adverse events (including serious adverse events [SAEs] and thrombovascular events [TVEs]), changes from baseline in clinical laboratory tests, changes from baseline in blood pressure and ECOG performance status scores at end of study, and physical examination findings.

Statistical Methods: Statistical significance for all efficacy endpoints were interpreted using $p \leq 0.05$, 2-sided.

Efficacy: The change in Hb at EOS was analyzed using an analysis of covariance (ANCOVA) model with treatment as the fixed effect and baseline Hb as the covariate, and a one-sided 95% confidence interval was estimated for the treatment group difference (80,000 U Q2W minus 40,000 U QW). The primary efficacy analysis was performed on both the per protocol population, consisting of all patients who had a change from baseline to EOS Hb value and no major protocol violations, and the mITT population, which included all randomized patients who received at least 1 dose of study drug and who had at least one Hb measurement post baseline. All secondary efficacy endpoints were analyzed using the mITT population.

Kaplan-Meier estimates were calculated for all time-to-event variables, and the corresponding distributions were compared between treatment groups using the log-rank test. Logistic regression with baseline Hb value as a covariate was used to analyze the proportions of patients achieving pre-specified Hb targets by week for Week 5 to 13, the proportion of patients with a ≥1 g/dL or ≥1.5 g/dL Hb increase within any 2-week study period (unrelated to pRBC transfusion), and the proportion of patients who received at least one pRBC transfusion during the prespecified time periods.

An ANCOVA model with treatment arms as the fixed effect and baseline Hb as the covariate was used to analyze the change from baseline in Hb values at each week and the number of pRBC units transfused per patient. Both last observation carried forward (LOCF) and an observed case (OC) approach were used to analyze the change in Hb over time.

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Efficacy (continued): The proportion of patients who had a change in dosing regimen (from Q2W to QW) was summarized descriptively. All Hb values obtained within 28 days following pRBC transfusion were set to missing for the efficacy analyses.

Safety: Safety data were analyzed for the safety/ITT population. Adverse events were summarized by body system, preferred term, and treatment group. Adverse events were also summarized by severity and relationship to study drug. Summary statistics (mean, standard deviation, median, and range) and changes from baseline were provided by treatment group for clinical laboratory tests and blood pressure measurements. A shift table of the change in ECOG performance status scores between baseline and EOS was provided by treatment group. Post hoc TVE and clinically relevant TVE (CR TVE) analyses pertaining to the incidence of Hb rate of rise and Hb greater than 13 g/dL included patients who received at least one dose of study drug and who had at least one post-dose Hb measurement.

SUMMARY – CONCLUSIONS

BASELINE ASSESSMENTS AND EXTENT OF EXPOSURE:

Of the 310 patients who were enrolled and randomized, 6 in each treatment group did not receive any study medication. Thus, 298 patients (153 in 80,000 U Q2W group, 145 in 40,000 U QW group) were randomized and received at least one dose of study drug (safety/ITT population), of whom 178 (59.7%) completed the study as planned. There were no notable differences in the reasons for study discontinuation between the epoetin alfa treatment groups. The 298 patients were mainly female (66.1%) and Caucasian (77.2%), and had a mean age of 62.4 years. The mean baseline Hb value was 9.95 g/dL and 9.96 g/dL in the 40,000 U QW and 80,000 U Q2W groups, respectively. Breast, lung and colorectal cancer were the most common tumor types at study entry. Demographic and baseline characteristics of patients assigned to the 80,000 U Q2W and 40,000 U QW epoetin alfa groups were similar.

Over the entire study, the mean cumulative dose of study drug was 304,706 U for the Q2W group and 340,621 U for the QW group, and the average number of doses of study treatment in these 2 groups was 4.1 and 8.1, respectively. Overall, the dose of epoetin alfa was required to be reduced for fewer patients in the 80,000 U Q2W group compared with the 40,000 U QW group (41% and 59%, respectively). Similarly, the dose of epoetin alfa was required to be withheld for fewer patients in the 80,000 U Q2W group compared with the 40,000 U QW group (21% and 42%, respectively).

EFFICACY RESULTS:

Primary efficacy endpoint: The LS mean change in Hb values from baseline to EOS in the 80,000 U Q2W epoetin alfa group (1.6 g/dL) was comparable to that in the 40,000 U QW epoetin alfa group (1.8 g/dL) (treatment difference [95% CI], -0.2 g/dL [-0.56, ---]) in the per protocol population (primary efficacy analysis set). The same was true for the mITT population (treatment group difference, 0.0 g/dL).

Secondary efficacy endpoints: After the first dose of study drug, the mean increase in Hb at Week 2 was significantly larger among patients receiving the 80,000 U dose (0.4 g/dL) compared with those receiving the 40,000 U dose (0.1 g/dL) ($p=0.005$). With continued treatment, however, mean increases in Hb were similar for both epoetin alfa groups ($p\geq0.066$). Kaplan-Meier estimates of the time to achieve Hb responses indicated no difference between the 80,000 U Q2W and 40,000 U QW epoetin alfa regimens. The median time to achieve at ≥1 g/dL rise in Hb was 22 days for the 80,000 U Q2W group compared with 29 days for the 40,000 U QW group ($p=0.392$). Beginning at Week 5, no differences were seen in the proportion of patients achieving various Hb responses throughout the study. By Week 13/Study End, 50% and 52% of patients in the 80,000 U Q2W and 40,000 U QW groups, respectively, had achieved a Hb increase of at least 2 g/dL.

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Secondary efficacy endpoints, continued: The proportion of patients receiving transfusions from Day 29 to Study End was 9.6% among patients assigned to the 80,000 U Q2W group and similar to the 40,000 U QW group (11.1%). The mean Hb prior to transfusion was 8.22 g/dL and 7.92 g/dL for the 80,000 U Q2W and 40,000 U QW groups, respectively. The Kaplan-Meier estimate of the proportions of patients who received pRBC transfusions from Week 5 to the end of study was 11.2% for the 80,000 U Q2W group and 12.0% for 40,000 U QW group; the difference between the proportions of two treatment groups was –0.7% and the 95% confidence interval of the difference was (-9.1%, 7.6%). The mean number of pRBC units transfused per transfused patient was less for the 80,000 U Q2W regimen than for the 40,000 U QW regimen (2.5 vs 3.4 units, respectively).

SAFETY RESULTS: Overall, treatment with 80,000 U Q2W or 40,000 U QW epoetin alfa was associated with similar safety profiles. Dosing epoetin alfa at a higher dose of 80,000 U on a Q2W regimen did not result in any unexpected adverse event(s) in this population of patients with cancer undergoing chemotherapy. The incidence of adverse events was similar between the 80,000 U Q2W (96%) and 40,000 U QW (94%) epoetin alfa groups, with the most frequently reported adverse events being diarrhea (20% and 28%, respectively), nausea (24% for each), and fatigue (25% and 20%, respectively). Most adverse events were judged by the investigator to be unrelated to study drug therapy, and only 2 patients had adverse events considered probably or very likely related to study treatment (bone pain, thrombocytopenia). A similar number of patients (n=17, 11-12%) in each treatment group were withdrawn from the study due to an adverse event, most of which were related to the patients' underlying cancer and not study drug.

The incidence of clinically relevant TVEs (CR TVEs) was similar (8%) in both the 80,000 U Q2W and 40,000 U QW groups, and only 2 CR TVEs (pulmonary embolism, deep vein thrombosis) were judged by the investigator to be related to study drug. In both treatment groups, the incidence of a TVE or CR TVE was similar among patients exhibiting a >1 g/dL rise in Hb over a 2-week period or a Hb rise to >13 g/dL versus those who did not exhibit either of these Hb changes (Table A).

Ten (6.5%) patients in the 80,000 U Q2W group and 9 (6.2%) in the 40,000 U QW group died as the result of an adverse event that had an onset between the start of treatment and 30 days after the last dose of study drug. Serious adverse events within the same time period occurred with a similar incidence in the 80,000 U Q2W (n=52, 34%) and 40,000 U QW (n=51, 35%) groups. The majority of deaths in both groups were related to disease progression, and most serious adverse events were related to the patients' underlying cancer or chemotherapy regimen.

There were no clinically meaningful differences between the 2 treatment groups in mean values over the course of the study for hematology, serum chemistry, or iron status parameters. There was little variation in vital sign measurements or physical examination findings during the study in either treatment group.

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Table A. Incidence of TVEs and CR TVEs Occurring with Hb Change (Safety Population)

	40,000 U QW (N=145)		80,000 U Q2W (N=153)	
Patients with at least 1 TVE, n (%)	16 (11.0)		13 (8.5)	
Patients with at least 1 CR TVE, n (%)	11 (7.6)		12 (7.8)	
Types of CR TVEs[a], n (%)				
Deep vein thrombosis	6		5	
Cerebrovascular accident	5		2	
Pulmonary embolism	1		2	
Angina pectoris	0		2	
Phlebothrombosis	0		1	
Myocardial infarction	0		1	
Thrombosis (not otherwise specified)	1		1[b]	
Hb rate of rise >1 g/dL in any 2-week period[c]	**Yes**	**No**	**Yes**	**No**
Number of patients	110	34	106	45
Incidence of TVE, n (%)[d]	9 (8.2)	7 (20.6)	10 (9.4)	3 (6.7)
Incidence of CR TVE, n (%)[d]	5 (4.6)	6 (17.7)	9 (8.5)	3 (6.7)
Hb >13 g/dL at any time[c]				
Number of patients	51	93	39	112
Incidence of TVE, n (%)[d]	4 (7.8)	12 (12.9)	3 (7.7)	10 (8.9)
Incidence of CR TVE, n (%)[d]	2 (3.9)	9 (9.7)	2 (5.1)	10 (8.9)

Note: The types of non-CR TVEs included the following for the 40,000 U QW group: chest discomfort, chest pain, and phlebitis, and for the 80,000 U Q2W group: phlebitis and chest pain.

[a] CR TVEs reported for more than 1 patient in either treatment group.

[b] Thrombosis in 80,000 U Q2W group subsequently was not clinically relevant since it was a superficial thrombosis.

[c] Hb changes may have occurred either before or after the TVE or CR TVE.

[d] Incidence calculated using number of patients with appropriate Hb response target as denominator.

CONCLUSION:

Initiating epoetin alfa treatment for chemotherapy-induced anemia with 80,000 U every 2 weeks provides similar efficacy with respect to hematopoietic response and transfusion utilization and similar safety as the currently approved epoetin alfa dosage of 40,000 U weekly.

Date of the report: 11-April-2006

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